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Metformin and Vitamin B12 Deficiency: Consequences and Patient Monitoring

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Abstract

- The incidence of type 2 diabetes has been increasing at a rapid rate in the United States.
- Metformin is recommended as the first line treatment to be started at the time of diagnosis in all patients without contraindications and has been associated with vitamin B12 deficiency.
- There are currently no clinical guidelines for the routine monitoring of B12 levels in this population.
- The purpose of this scholarly project is to determine if there are consequences of this deficiency and to make recommendations for screening patients.
- It includes current research that focuses on the pathophysiology of a B12 deficiency, the prevalence and consequences of such a deficiency, and practices in monitoring patients for it.
- While many type 2 diabetics treated with metformin will develop a vitamin B12 deficiency, there may not be any consequences of this deficiency.
- More research is needed before universal guidelines can be established. At this point in time, monitoring B12 levels should be a decision based on individual patient's risk factors and symptoms.

Introduction

- From 1980 through 2014, the number of people diagnosed with diabetes mellitus has increased from 5.5 to 22 million (Centers for Disease Control and Prevention, 2014). Of these, 90-95% have type 2 diabetes mellitus.
- Most global guidelines recommend starting metformin in patients with no contraindications at the time of diagnosis due to its efficacy, safety, and cost.
- There have been numerous studies that have suggested a relationship between metformin use and decreased vitamin B12 levels at a rate of 5.8-22.6% (de Groot-Kamphius et al., 2013).
- While not fully understood, it is hypothesized that it could be occurring due to an impaired calcium dependent absorption of intrinsic factor and vitamin B12 in the ileum, an altered motility of the small intestine, a decrease in the acidity of the stomach, or an alteration in the normal flora of the gut (Kibridge & Mwebaze, 2013).
- The purpose of this scholarly project is to establish a link between metformin use in type 2 diabetics and vitamin B12 deficiency, explore the consequences of such a deficiency, and make recommendations as to who should be screened.

Statement of the Problem

- While the link between metformin and decreased vitamin B12 levels has been well established in literature, there are no clinical guidelines addressing routine evaluation for this condition in type 2 diabetics taking this medication.
- In addition, the effects of such a deficiency in this patient population has not been well established.

Research Questions

- In adult patients with type 2 diabetes taking metformin, does a vitamin B12 deficiency cause adverse effects?
- In this same population, should routine screening for a vitamin B12 deficiency be performed?

Literature Review

Physiologic Role of Vitamin B12 and Pathophysiology of a Deficiency

- Functions:
  - Necessary for the methylation of homocysteine to methionine, which is activated into S-adenosyl-methionine and gives a methyl group to methyl acceptors such as myelin, neurotransmitters, and membrane phospholipids
  - Necessary for the conversion of methylmalonyl coenzyme A (CoA) to succinyl CoA which is involved in the synthesis of neuronal membranes
  - Required for DNA synthesis, hematopoiesis, and cellular repair
- Vitamin B12 Deficiency**:**
  - Hyperhomocysteinemia which has a damaging effect on vascular endothelium and neurons
  - An increase in methylmalonic acid (MMA) leading to a defective synthesis of fatty acids in neuronal membranes
  - Fatigue, depression, impaired cognition
  - Macrocytic anemia
  - Glossitis, stomatitis and malabsorption
  - Demyelination, degeneration, and death of axons manifesting as peripheral and/or autonomic neuropathy, delirium, dementia, or a subacute degeneration of the spinal cord

(Kibridge & Mwebaze, 2013)

Metformin and Vitamin B12 Deficiency

- A meta-analysis performed by Niafar, et al. (2015) found that metformin treated groups had lower vitamin B12 levels ($p<0.00001$) as well as a higher incidence of vitamin B12 deficiency (OR 2.45, 95% CI 1.74-3.44, $p<0.00001$).
- De Jager, et al. (2010) found the decrease in B12 levels to be progressive over time and homocysteine levels increased as B12 levels decreased.
- Using data from the Diabetes Prevention Program Outcomes Study, Aroda et al. (2016) found the only statistically significant predictor of vitamin B12 deficiency was the total years of exposure to metformin.
- Beulens et. al (2015) found higher daily doses ($p<0.001$) and higher cumulative doses ($p<0.022$) were associated with lower vitamin B12 and holotranscobalamin levels.
- Ko et al. (2014) found those taking metformin in larger doses (>1,000 mg/day) and for a longer duration (>4 years) had a greater prevalence of vitamin B12 deficiency ($p<0.001$).

Diagnostic studies that Assess for a Vitamin B12 Deficiency

- No gold standard
- Serum B12 levels: recently ingested B12; does not detect deficiency at tissue level (Pagana & Pagana, 2014); not very specific or sensitive (Salwen, 2017)
- Homocysteine: can elevate before vitamin B12 levels are abnormal (Pagana & Pagana, 2014)
- Methylmalonic acid (MMA): measured in urine or serum; elevation reveals a more longstanding deficiency (Pagana & Pagana, 2014)
- Holotranscobalamin: protein that binds up to 25% of circulating B12 and delivers it to the tissues; newer method hypothesized to be more sensitive in determining a deficiency at the cellular level (Beulens, et al., 2015).

Effects of a Metformin Induced Vitamin B12 Deficiency on Patients

- Adaikalakotswari, et al. (2014) found triglycerides and cholesterol/HDL ratios were inversely related to vitamin B12 levels but did not find a relationship between B12 levels and other diabetic co-morbidities such as retinopathy, neuropathy, nephropathy, cerebrovascular accident, and peripheral vascular disease.
- Hansen, et al. (2016) found vitamin B12 levels to be inversely related to cardiac autonomic neuropathy.
- Aroda, et al. (2016) found that homocysteine levels were increased in those with low or borderline low vitamin B12 levels. At year 9 of the study, anemia in the metformin group was slightly increased in those with lower B12 levels but was not significant ($p=0.25$).
- Chen, et al. (2012) used multiple methods to assess for neuropathy and were unable to find a significant relationship between peripheral neuropathy and vitamin B12 levels.
- Singh, et al. (2013) found the duration of metformin use to be positively related to neuropathy score (95% CI 0.35-0.65, $p<0.001$).

Current Vitamin B12 Monitoring in Type 2 Diabetics taking Metformin

- Pierce, Chung, & Black (2012) looked at subjects taking metformin. Only 40% of the total subjects had a vitamin B12 measured and 46% of patients who had been on high dose metformin greater than 10 years had never had one assessed. 29% with newly diagnosed anemia and 42% with newly documented neuropathy did not have a vitamin B12 level measured.
- Farland, et al (2015) found those with symptoms or a diagnosis of macrocytic anemia or peripheral neuropathy were more likely to have a vitamin B12 level measured than those in the control group (OR 5.83, 95% CI 3.47-9.77, $p<0.001$), but it was only 48.3% of these patients.

Discussion

- Symptoms of B12 deficiency are similar to type 2 diabetes complications.
- Future studies considering the effect of vitamin B12 deficiency on type 2 diabetics without considering the use of metformin would be beneficial.
- Conflicting results in regards to the predictors for a deficiency to occur, such as duration of treatment, size of dose, and cumulative doses have been observed.
- Diet, other comorbidities, or medications can also contribute to a deficiency.
- Unless the prevalence of a metformin induced vitamin B12 deficiency is defined more clearly or stronger evidence of consequences is found, routine screening of all diabetics may not be warranted.
- Screening should be considered in those patients who are taking higher doses of metformin (>1000 mg/day) or for longer durations (>4 years).
- Vitamin B12 status should be assessed if symptoms of a deficiency are evident.
- Screening is not recommended to be performed yearly as the stores in the liver can last anywhere from 3 to 6 years.

Applicability to Clinical Practice

- Patients who are already at risk for a deficiency, such as those who are on long term PPIs, abuse alcohol, vegetarians, or are malnourished, should be monitored more closely for symptoms of a B12 deficiency.
- For those patients not already at a risk for a deficiency, assess for symptoms of a deficiency prior to initiation of the medication as well as at regular follow up visits.
- Consider a B12 deficiency in the differential diagnosis when symptoms such as peripheral neuropathy, anemia, and cardiovascular disease present rather than attributing these symptoms to the diabetes.
- Vitamin B12 is water soluble and the excess is excreted in the urine so there is little risk of supplementing with B12 in patients with adequate renal function even if they are not deficient.

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